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Dated: January 22, 2008 Signature: Pamela Harrison
(Pamela A. Harrison)

Docket No.: ALEX-P01-054
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Bowdish et al.

Application No.: 10/006,593 Confirmation No.: 3532

Filed: December 5, 2001 Art Unit: 1643

For: RATIONALLY DESIGNED ANTIBODIES Examiner: P. K. Tungaturthi

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Declaration Under 37 C.F.R. §1.132 of James D. Marks

Sir:

I, James D. Marks of Kensington, California, hereby declare as follows:

1. I am currently a Professor of Anesthesia and Pharmaceutical Chemistry at the University of California, San Francisco Comprehensive Cancer Center. I have an M.D. and a Ph.D. in Molecular Biology. A copy of my curriculum vitae is attached as Exhibit A. I was previously a member of the Scientific Advisory Board of Alexion Pharmaceuticals, Inc., the assignee of Application No. 10/006,593. I have over 20 years of scientific research experience with an emphasis in molecular biology and immunology and have over 130 scientific publications.

2. I have reviewed the pending Application No. 10/006,593, the pending claims, the Office Action dated July 25, 2007, and the cited references Barbas(a) (WO94/18221), Barbas(b) (PNAS 92:2529-2533, 1995), Cwirla et al. (Science 276:1696-1699, 1997), Dower et al. (WO 96/40750), Helms (Protein Science 4:2073-2081, 1995) and Wrighton et al. (Science 273:458-463, 1996).

3. The Barbas references disclose immunoglobulin molecules with engineered polypeptide or DNA binding sites. The engineered binding site is introduced into a CDR region of an

immunoglobulin molecule. The modified immunoglobulin molecule, in turn, is able to bind a polypeptide or DNA molecule through the engineered binding site. All the molecules taught by the Barbas references merely bind their target and block the binding of endogenous ligands, therefore acting as antagonists.

4. A receptor antagonist binds to a receptor, such as a thrombopoietin (TPO) or erythropoietin (EPO) receptor, and prevents the activation of the receptor by an agonist-ligand. There are a number of different means by which a molecule can function as a receptor antagonist. The antagonist may bind at the same or overlapping binding site of the agonist and physically prevent the interaction between the receptor and agonist. The antagonist may bind at a completely different site on the receptor, but due to its large size the antagonist may still physically prevent the interaction between the receptor and agonist. The antagonist could also disrupt binding between the receptor and another protein involved in receptor activation, for example, it could prevent homo- or hetero-dimerization of the receptor. The antagonist may bind the receptor and induce a conformational change in the receptor which prevents it from binding agonist.

5. In contrast, a receptor agonist activates a receptor. Mere binding is not sufficient, but rather an agonist must induce a very specific conformational change in the receptor in order to transduce an activating signal. There are, therefore, more constraints on a molecule for it to function as an agonist rather than an antagonist. The TPO and EPO receptors belong to the Class I cytokine receptor family, which requires dimerization for activation. Studies have demonstrated that activation is in fact dependent on the specific configuration of the agonist-receptor dimer complex. For example, Wilson et al. (Curr. Opin. Struct. Biol. 9: 696-704 (1999); submitted herewith as Exhibit B) reviews studies performed on the EPO receptor as a model for receptor activation in this receptor family. The configuration of the receptor assembly (receptor plus bound ligand) was found to affect the efficiency of receptor activation. It was also found that the orientation of the monomer receptor within the assembly affects receptor signaling (see page 697, left column, first full paragraph) and that the ligand (agonist) induces receptor reorganization (see page 700, right column, end of first partial paragraph).

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6. Certain claims presented in Application No. 10/006,593 are to EPO and TPO receptor agonists. While the peptides from Cwirla et al. and Wrighton et al. function as agonists, prior to the invention disclosed in the present application there was no reason to expect that when placed within a CDR region of an antibody they would retain the same function. For antagonist peptides inserted into a larger protein scaffold, all that needs to be maintained is binding ability. Indeed the larger size could also have been expected to enhance the antagonist activity because it may increase steric interference. However, based on the more complex nature of receptor activation, it would not have been expected that an agonist peptide inserted into a protein scaffold would maintain its activity in the same manner as an antagonist peptide. Instead, modification of an agonist peptide in this manner would have been expected to interfere with the agonist activity of the peptide.

7. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title XVIII of the United States Code and that willful false statements may jeopardize the validity of this Application for Patent or any patent issuing thereon.

James D. Marks M.D., Ph.D.

Dated: 1/18/08 Signature: James D Marks MD PhD